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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/658,782	09/08/2003	Phillip Arcangel	PP-19199.002	7355
27476	7590	01/26/2005	EXAMINER	
Chiron Corporation Intellectual Property - R440 P.O. Box 8097 Emeryville, CA 94662-8097			MCGAW, MICHAEL M	
		ART UNIT	PAPER NUMBER	1648

DATE MAILED: 01/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/658,782	ARCANGEL ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Michael M. McGaw	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 18 Nov 2004.
- 2a) This action is **FINAL**.                    2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 3,6-16,19 and 22-34 is/are pending in the application.
- 4a) Of the above claim(s) 33 and 34 is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 3,7-14,19 and 21-30 is/are rejected.
- 7) Claim(s) 6, 15, 16, 22, 31, 32 is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All    b) Some \* c) None of:
1. Certified copies of the priority documents have been received.
  2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | Paper No(s)/Mail Date. _____  |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
|  | 6) <input checked="" type="checkbox"/> Other: <u>Sequence Alignment</u> .   |

## **DETAILED ACTION**

Claims 1-32 were pending in the prior Office Action mailed August 13, 2004. Applicant has cancelled claims 1, 2, 4, 5, 17, 18, 20 and 21 in Applicant's response received November 18, 2004. Applicant has amended claims 3, 6, 15, 16, 19, 22, 31 and 32. Applicant has added claims 33 and 34. Claims 3, 6-16, 19 and 22-34 are currently pending.

### ***Election/Restrictions***

Newly submitted claims 33 and 34 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 33 and 34 depend upon previously rejected claims 3 and 19. Claims 3 and 19 were rejected in the previous Office Action under 35 U.S.C. 103(a) as being unpatentable over Chien et al. (1999) in view of U.S. Patent No. 6,306,579 B1 to Seidel et al. Claims 3 and 19 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Chien et al. (1999) in view of U.S. Patent No. 6,306,579 B1 to Seidel et al. and Choo, Q.L. et al. (1991). Claims 33 and 34 do not include all the limitations of previously searched subject matter deemed allowable and thus are beyond the scope of that which was previously searched.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 33 and 34 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

***Claim Rejections - 35 USC § 112, ¶2***

The rejection of claims 1, 2, 3 and 6 under 35 U.S.C. 112, 2<sup>nd</sup> paragraph is withdrawn pursuant to Applicant's amendments and explanations.

Applicant has removed the use of the term "first region" from the claims, rendering this rejection moot. Applicant has redefined the term "epitope" in the specification and more fully explained their definition. Applicant has amended the claims to resolve the issue of an incompatible combination of closed language in the dependent claim followed by open claim language directed to the same term in dependent claims therefrom. Applicant has amended claims 6, 15, 16, 22, 31, and 32, thereby clarifying them, by removing references to figures, with sequence identification numbers in parentheses, and referred solely to the sequence identification number. Applicant has addressed the issues raised as to claims 9 and 25 by pointing to the fact that the underlying sequence includes a combination of previously defined epitopes, thus evidencing the operability of the epitopes.

***Claim Rejections - 35 USC § 103***

1. Claims 1-5, 7-14, 17-21, 23-25 and 26-30 were rejected in the previous Office Action under 35 U.S.C. 103(a) as being unpatentable over Chien et al. (1999) in view of U.S. Patent No. 6,306,579 B1 to Seidel et al. Claims 1, 2, 4, 5, 17, 18, 20 and 21 were cancelled rendering moot their rejection. Claims 3 and 19 have been amended to obviate the prior rejection. Thus, the prior rejection of claims 3, 7-8, 10-14, 19, 23-24

and 26-30 over Chien et al. (1999) in view of U.S. Patent No. 6,306,579 B1 to Seidel et al. is withdrawn.

2. Claims 3, 7-8, 10-14, 19, 23-24 and 26-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chien et al. (1999) in view of U.S. Patent No. 6,306,579 B1 to Seidel et al. and Choo, Q.L. et al. (1991).

Applicant indicates that claims 3 and 19, from which all claims depend, have been amended to import limitations from claims 6 and 22, whereby the claim recites the limitation of SEQ ID NO:2. In fact, the claims do not include the limitation of SEQ ID NO:2, but rather "*at least 80% sequence identity* to the contiguous amino acid sequence of SEQ ID NO:2."

The claims are drawn to a method of detecting hepatitis C virus infection using a multiple epitope fusion antigen (MEFA) where the MEFA comprises at least one epitope in common with an NS3/4a antigen and either the antigen or the MEFA is used as the solid support. As mentioned above, Applicant has further amended the base claims 3 and 19 to obviate the prior rejection by adding the limitation wherein the NS3/4a antigen has an amino acid sequence with at least 80% sequence identity to the contiguous amino acid sequence of SEQ ID NO:2. Claims subsequent to claim 3 require that the MEFA and the antigen to possess at least one epitope from a specific region of the NS3/4a region. Claims 3, 6-16 and 33 are directed to a system whereby it is the "one or more NS3/4a antigens" that are bound to the solid support and the MEFA is subsequently added; a version of a double antigen bridge test. Claims 19 and 22-32 are

directed to a system whereby it is the MEFA bound to the solid support and it is the one or more antigens that are subsequently added; also a double antigen bridge.

Chien et al. (1999) Journal of Clinical Microbiology, vol. 37, No..5; p. 1393-97 teach a method of detecting hepatitis C virus infection in a biological sample using a MEFA containing all of the major immunogenic epitopes of HCV where the MEFA comprises at least one epitope in common with the antigen used in the solid support. (See abstract) Chien et al. (1999) is discussed more fully in the previous action. It was pointed out that Chien et al. (1999) did not employ a double antigen bridge test. As indicated in the previous Office Action in regards to claims 9 and 25, Figure 1 of Chien et al. (1992) on page 10012 indicates that the C33C polypeptide which was part of Chien's C25 chimeric polypeptide is derived from the NS3 region. Also on page 10012 Chien indicates that "the C33C polypeptide . . . is derived from most of the NS3 region that appears to encode both a viral protease and a helicase." (See the last full line of col. 1) Thus, it teaches or suggests the region from 1193-1657 as found in claims 9 and 25. Chien does not provide the particular sequence of his antigen across the NS3/4a region.

Also as indicated in the previous action, U.S. Patent No. 6,306,579 B1 ('579) teaches a double antigen bridge test using HCV antigens from the NS3 region in immunological tests (See col. 4, lines 16-25). The '579 patent indicates that, when compared to other formats, a double antigen bridge results in both increased sensitivity (other immunoglobulin classes are recognized) and increased specificity (fewer unspecific reactions are seen).

Choo, Q.L. et al. (1991) teaches the amino acid sequence of the HCV polyprotein. Choo's sequence is 99.5% identical to Applicant's SEQ ID NO. 2. See also the sequence alignment printout included with the present Office Action.

One of ordinary skill in the art would have been motivated to combine the teachings of Chien with those of the '579 patent to create an immunological test for the detection of HCV-specific antibodies using a MEFA in a double antigen bridge format because the '579 patent et al indicates that the double antigen bridge format results in increased specificity and sensitivity. Moreover, at 99.5% identity, Choo's published sequence falls squarely within Applicant's parameters of 80% sequence identity to the contiguous amino acid sequence of SEQ ID NO:2. One of ordinary skill in the art would have expected to produce an immunological test for the detection of HCV-specific antibodies using MEFAs with enhanced sensitivity because Chien et al. teaches the efficacy of MEFAs in binding HCV-specific antibody while the '579 patent teaches the improved performance of the double antigen bridge format in the context of an immunological test for HCV-specific antibody to the NS3 region. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

3. Claims 9 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chien et al. (1999) in view of U.S. Patent No. 6,306,579 B1 to Seidel et al. and Choo, Q.L. et al. (1991) as applied to claims 3, 7-8, 10-14, 19, 23-24 and 26-30 above, and further in view of Chien et al. (1992).

Claims 9 and 25 indicate that the MEFA comprises amino acids 1193-1657 of the HCV sequence. This is the portion of NS3 that corresponds to the helicase region.

Figure 1 of Chien et al. (1992) on page 10012 indicates that the C33C polypeptide which was part of Chien's C25 chimeric polypeptide is derived from the NS3 region. Also on page 10012 Chien indicates that "[t]he C33C polypeptide ... is derived from most of the NS3 region that appears to encode both a viral protease and a helicase." (See the last full line of col. 1) It is not clear from the disclosure whether Chien included the entire helicase region in his MEFA, as currently claimed by applicant, but the statement certainly strongly suggests its inclusion.

One of ordinary skill in the art would have been motivated to include the helicase peptide in a MEFA containing epitopes directed against the NS3/4a region of the HCV polypeptide because Chien et al. showed the efficacy of helicase epitopes and indicated the importance of the inclusion of antigenic determinants from the helicase region. One of ordinary skill in the art would have expected to produce a MEFA capable of detecting antibody specific to the helicase region because Chien et al. teaches the efficacy of such an epitope in a MEFA. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

4. Claims 1-5, 7-8, 10-21, 23-24 and 26-32 were rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,428,792 B1 ('792) to Valenzuela in view of U.S. Patent No. 6,306,579 B1 ('579) to Seidel. Claims 15, 16, 31 and 32 were further rejected under 35 U.S.C. 103(a) over Valenzuela in view of Seidel as outlined on page

10 of the prior action. These rejections are withdrawn pursuant to Applicant's cancellation of claims 1, 2, 4, 5, 17, 18, 20 and 21 and Applicant's amendment of claims 3 and 19 adding the limitation directed at identity to SEQ ID NO:2.

5. Claims 3, 7-8, 10-14, 19, 23-24 and 26-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Pat. No. 6,428,792 to Valenzuela et al. in view of U.S. Patent No. 6,306,579 B1 to Seidel et al. and Choo, Q.L. et al. (1991).

Valenzuela et al. (US Pat. No. 6,428,792 B1) teach a method of detecting hepatitis C virus infection in a biological sample using a MEFA containing all of the major immunogenic epitopes of HCV where the MEFA comprises at least one epitope in common with the antigen used in the solid support (See abstract) Valenzuela's MEFA-3, MEFA-5 and MEFA-6 chimeric polypeptides included epitopes from the NS3(protease)/NS4a(helicase) region (see fig. 1A-1C). Valenzuela employed a system whereby the MEFA was coated on the plates, test sample containing anti-HCV antibody was added, and then conjugated antibody was added to detect the anti-HCV antibody bound to the MEFA. Thus, Valenzuela et al did not employ a double antigen bridge test.

Seidel et al teach a double antigen bridge test using HCV antigens from the NS3 region in immunological tests (U.S. Pat. No. 6,306,579 B1). (See col. 4, lines 16-25). Seidel indicates that, when compared to other formats, a double antigen bridge results in both increased sensitivity (other immunoglobulin classes are recognized) and increased specificity (fewer unspecific reactions are seen).

Choo, Q.L. et al. (1991) teaches the amino acid sequence of the HCV polyprotein. Choo's sequence is 99.5% identical to Applicant's SEQ ID NO. 2. See also the sequence alignment printout included with the present Office Action.

One of ordinary skill in the art would have been motivated to combine the teachings of Valenzuela with those of Seidel to create an immunological test for the detection of HCV-specific antibodies using MEFA in a double antigen bridge format because Seidel et al indicates that the double antigen bridge format results in increased specificity and sensitivity. One of ordinary skill in the art would have expected to produce an immunological test for the detection of HCV-specific antibodies using MEFAs with enhanced sensitivity because Valenzuela et al. teaches the efficacy of MEFAs in binding HCV-specific antibody while Seidel teaches the improved performance of the double antigen bridge format in the context of an immunological test for HCV-specific antibody to the NS3 region. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

6. Claims 9 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Pat. No. 6,428,792 to Valenzuela et al. in view of U.S. Patent No. 6,306,579 B1 to Seidel et al. and Choo, Q.L. et al. (1991) as applied to claims 3, 7-8, 10-14, 19, 23-24 and 26-30 above, and further in view of Chien et al. (1992).

Claims 9 and 25 indicate that the MEFA comprises amino acids 1193-1657 of the HCV sequence. This is the portion of NS3 that corresponds to the helicase region.

Figure 1 of Chien et al. (1992) on page 10012 indicates that the C33C polypeptide which was part of Chien's C25 chimeric polypeptide is derived from the NS3 region. Also on page 10012 Chien indicates that "[t]he C33C polypeptide ... is derived from most of the NS3 region that appears to encode both a viral protease and a helicase." (See the last full line of col. 1) It is not clear from the disclosure whether Chien included the entire helicase region in his MEFA, as currently claimed by applicant, but the statement certainly strongly suggests its inclusion.

One of ordinary skill in the art would have been motivated to include the helicase peptide in a MEFA containing epitopes directed against the NS3/4a region of the HCV polypeptide because Chien et al. showed the efficacy of helicase epitopes and indicated the importance of the inclusion of antigenic determinants from the helicase region. One of ordinary skill in the art would have expected to produce a MEFA capable of detecting antibody specific to the helicase region because Chien et al. teaches the efficacy of such an epitope in a MEFA. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

7. Claims 1-5, 7-14, 17-21 and 23-30 were rejected under 35 U.S.C. 103(a) as being unpatentable over Chien et al. (1992) in view of Seidel et al. These rejections are withdrawn pursuant to Applicant's cancellation of claims 1, 2, 4, 5, 17, 18, 20 and 21 and Applicant's amendment of claims 3 and 19 adding the limitation directed at identity to SEQ ID NO:2.

8. Claims 3, 7-14, 19 and 23-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chien et al. (1992) in view of U.S. Patent No. 6,306,579 B1 to Seidel et al. and Choo, Q.L. et al. (1991).

The claims are drawn to a method of detecting hepatitis C virus infection using a multiple epitope fusion antigen (MEFA) where the MEFA comprises at least one epitope in common with an antigen and either the antigen or the MEFA is used as the solid support. Claims subsequent to claim 1 require that the MEFA and the antigen to possess at least one epitope from the NS3/4a region or a specific region of the NS3/4a region.

Chien et al. (1992) Proc. Nat. Acad. Sci., vol. 89; pp. 10011-10015 teach an immunodominant chimeric polyprotein, which would also constitute a MEFA, using regions from NS3, NS4 and C of HCV to be used in assays formats such as ELISAs. The epitopes in one of the chimeric polyproteins, designated c25, is shown in fig. 1 on page 10012. The c25 polyprotein contained epitopes from the the NS3(protease)/NS4a(helicase) region. Chien et al did not employ a double antigen bridge test. Claims 9 and 25 indicate that the MEFA comprises amino acids 1193-1657 of the HCV sequence. This is the portion of NS3 that corresponds to the helicase region. Figure 1 of Chien et al. (1992) on page 10012 indicates that the C33C polypeptide which was part of Chien's C25 chimeric polypeptide is derived from the NS3 region. Also on page 10012 Chien indicates that "[t]he C33C polypeptide ... is derived from most of the NS3 region that appears to encode both a viral protease and a helicase." (See the last full line of col. 1) It is not clear from the disclosure whether

Chien included the entire helicase region in his MEFA, as currently claimed by applicant, but the statement certainly strongly suggests its inclusion.

Seidel et al teach a double antigen bridge test using HCV antigens from the NS3 region in immunological tests (U.S. Pat. No. 6,306,579 B1). (See col. 4, lines 16-25). Seidel indicates that, when compared to other formats, a double antigen bridge results in both increased sensitivity (other immunoglobulin classes are recognized) and increased specificity (fewer unspecific reactions are seen).

Choo, Q.L. et al. (1991) teaches the amino acid sequence of the HCV polyprotein. Choo's sequence is 99.5% identical to Applicant's SEQ ID NO. 2. See also the sequence alignment printout included with the present Office Action.

One of ordinary skill in the art would have been motivated to combine the teachings of Chien with those of Seidel to create an immunological test for the detection of HCV-specific antibodies using MEFA in a double antigen bridge format because Seidel et al indicates that the double antigen bridge format results in increased specificity and sensitivity. One of ordinary skill in the art would have expected to produce an immunological test for the detection of HCV-specific antibodies using MEFAs with enhanced sensitivity because Chien et al. teaches the efficacy of MEFAs in binding HCV-specific antibody while Seidel teaches the improved performance of the double antigen bridge format in the context of an immunological test for HCV-specific antibody to the NS3 region. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

9. The rejection of claims 6, 15, 16, 22, 31 and 32 under 35 U.S.C. 103(a) as being unpatentable over WO200196870-A2 to Chien et al. in view of U.S. Patent No. 6,306,579 B1 to Seidel et al. is withdrawn in view of Applicant's declaration regarding inventorship filed with the present response on November 18, 2004.

***Double Patenting***

The following obviousness-type double patenting rejections from the previous action is ***maintained***:

Claims 1-30 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 6,428,792 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application are broadly directed at methods of using MEFAs, while the claims of the patent are directed to broad product claims for MEFAs while disclosing the utility of such MEFAs in exactly the immunoassay format claimed in the methods of the present application. Furthermore, the MEFA claims of the prior patent read on the MEFAs disclosed in the methods of the present application. See for instance claims 1, 17.

The following obviousness-type double patenting rejections are made in the present Office Action:

Claims 3, 6-16, 19, and 22-32 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-21 of U.S.

Patent No. 6,632,601. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '601 patent claims a methods of detecting HCV using an immunoassay employing NS3/4a where the sequence of the NS3/4a is 100% identical to SEQ ID NO:2. See for instance claim 19.

Claims 3, 6-16, 19, and 22-32 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S.

Patent No. 6,797,809. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '809 patent claims a MEFA and teaches its use in immunoassays involving NS3/4a.

Claims 3, 6-16, 19, and 22-32 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S.

Patent No. 6,630,298. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '298 patent claims an immunoassay involving NS3/4a and MEFAs and methods of use therof. See for instance claim 9.

Claims 3, 6-16, 19, and 22-32 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-58 of copending Application No. 10/643,853. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications involve the use of MEFAs and NS3/4a in immunoassays.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 3, 6-16, 19, and 22-32 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-49 of copending Application No. 10/174,652. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications involve the use of MEFAs and NS3/4a in immunoassays.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 3, 6-16, 19, and 22-32 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 29-47 of copending Application No. 10/899,716. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications involve the use of MEFAs and NS3/4a in immunoassays.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

#### ***Allowable Subject Matter***

Claim 6, 15, 16, 22, 31 and 32 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The following is a statement of reasons for the indication of allowable subject matter: Claims 6 and 22 specify that the Ns3/4a sequence is SEQ ID NO: 2. The sequence is free of the prior art. SEQ ID NO: 2 was created by a contiguous 2 amino

acid change whereby the residues CS or CA, as found in the "5-1-1" region of the HCV polyprotein, were substituted with the contiguous residues PI. (See page 36 of the specification) The closest prior art is Choo et al. discussed above and teaching an amino acid sequence 99.5% identical to Applicant's SEQ ID NO:2 and Chien et al. (1992) teaching the use of a fused, chimeric polyprotein (C25) composed of the NS3, NS4 and the C regions of HCV in an immunoassay. SEQ ID NO: 4 is taught in U.S. Patent Nos. 6,630,298 which is commonly assigned. A double patenting rejection has been made. SEQ ID NO: 6 is taught in U.S. Patent Nos. 6,632,601 which is commonly assigned. A double patenting rejection has been made. SEQ ID NO:4 or SEQ ID NO:6 with the limitations of the rejected base claims is otherwise free of the prior art.

### ***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

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the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

m.m.

Michael M. McGaw

Sunday, January 23, 2005

*James C. House*  
JAMES HOUSE 1/24/05  
SUPERVISORY PATENT EXAMINER  
TECHNOLOGY CENTER 1600

DR; InterPro; IPR002522; HCV_capsid.	Qy 1 MAPITAYAQOTRGGLGCIITSLTGRDKNQVEGEVQIVSTAQTPLATCINGVCTVYHGA 60	Db 1026 LAPTTAYAQOTRGGLGCIITSLTGRDKNQVEGEVQIVSTAQTPLATCINGVCTVYHGA 1085
DR; InterPro; IPR002519; HCV_core.	Qy 61 GTRITASPKGPVIOMTYNDQDLVWPAQGSRSLTPCTCGSSPDLYLTVRHDVTPVRR 120	Db 1086 GTRITASPKGPVIOMTYNDQDLVWPAQGSRSLTPCTCGSSPDLYLTVRHDVTPVRR 1145
DR; InterPro; IPR002531; HCV_NS1.	Qy 121 GDSRGSSLSPRPISYLGKGGGPULLCPAGAVGIFRAAIVTRGVAKAVDIFPVENLETTM 180	Db 1146 GDSRGSSLSPRPISYLGKGGGPULLCPAGAVGIFRAAIVTRGVAKAVDIFPVENLETTM 1205
DR; InterPro; IPR002518; HCV_NS2.	Qy 181 RSPVFTDNSSPPVYVQSFQVAYHAPTGSKSTKVPAAYQKVLTINPSVATLGFF 240	Db 1206 RSPVFTDNSSPPVYVQSFQVAYHAPTGSKSTKVPAAYQKVLTINPSVATLGFF 1265
DR; InterPro; IPR000745; HCV_NS4A.	Qy 241 AYMSKAHGIDPNIIRTGVRITTTGSPITYSTYKGKFLADGGCSGGAYDIIICDECHSTDATAS 300	Db 1266 AYMSKAHGIDPNIIRTGVRITTTGSPITYSTYKGKFLADGGCSGGAYDIIICDECHSTDATAS 1325
DR; InterPro; IPR001490; HCV_NS4B.	Qy 301 ILGIGTVLDQAEETGARLVLTLATATPGSUTVPHNIEVALSTGIEIPPYKAIPEVYI 360	Db 1326 ILGIGTVLDQAEETGARLVLTLATATPGSUTVPHNIEVALSTGIEIPPYKAIPEVYI 1385
DR; InterPro; IPR002166; HCV_RdRp.	Qy 361 KGGRHLIIFCHSKKKCDELAARKLVAGINAVAYTRGLDVSVTIPGDDVVVATDALMTGYT 420	Db 1386 KGGRHLIIFCHSKKKCDELAARKLVAGINAVAYTRGLDVSVTIPGDDVVVATDALMTGYT 1445
DR; InterPro; IPR001650; HeIcase_C.	Qy 421 GDFDSVTDNCNTCVTQVDFSLDPTFTIETITLPOAVSRTORRGRTGRGPQIYRFVAPG 480	Db 1446 GDFDSVTDNCNTCVTQVDFSLDPTFTIETITLPOAVSRTORRGRTGRGPQIYRFVAPG 1505
DR; InterPro; IPR007095; RNA_Pol_DS_PS.	Qy 481 ERPSGMFDSSVLCBQYDAGAWYELTPAETTVRLRAYNTPGLPYCQDHLEFWEGVFTGL 540	Db 1506 ERPSGMFDSSVLCBQYDAGAWYELTPAETTVRLRAYNTPGLPYCQDHLEFWEGVFTGL 1565
DR; InterPro; IPR007094; RNA_Pol_PSVir.	Qy 541 THIDAHFLSQTKQSCBNLPVAVAOATVCAQAOPPSNDQMKCLIRLKPTLQAGPTPLL 600	Db 1566 THIDAHFLSQTKQSCBNLPVAVAOATVCAQAOPPSNDQMKCLIRLKPTLQAGPTPLL 1625
PFam; PF01543; HCV_capsid; 1.	Qy 601 YRLGAVQNEITLTHVTKYIMTCMSADLEYVTSTVNLVGGVLAALAYCLSTGCVIVGR 660	Db 1626 YRLGAVQNEITLTHVTKYIMTCMSADLEYVTSTVNLVGGVLAALAYCLSTGCVIVGR 1685
PFam; PF01542; HCV_core; 1.	Qy 661 VVLSCGPALIPDREVLYREFDEMBC 686	Db 1686 VVLSCGPALIPDREVLYREFDEMBC 1711
DR; Pfam; PF01539; HCV_env; 1.	RESULT 2 POLG_HCVH ID POLG_HCVH STANDARD: PRT; 3011 AA.	
DR; Pfam; PF01560; HCV_env; 1.	AC P27938; Rel. 23, Created)	DT 01-AG-1992 (Rel. 23, Last sequence update)
DR; Pfam; PF01538; HCV_NS1; 1.	DT 01-AG-1992 (Rel. 42, Last annotation update)	DT 10-Oct-2003 (Rel. 42, Last annotation update)
DR; Pfam; PF02907; HCV_NS3; 1.	DB Genome polyprotein [Contents]: Capsid Protein C (core protein) (P22); Envelope glycoprotein E1 (GP22); Envelope glycoprotein E2 (GP68). (GP70) (NS1); Protein P7; Nonstructural protein NS2 (P21); Protease/helicase NS3 (P70) (Replicase).	DB (EC 3.4.21.98); Nonstructural Protein NS4A (P4); Nonstructural Protein NS4B (P22); Nonstructural Protein NS5A (P56); Nonstructural Protein NS5B (P66) (P70) (RNA-directed RNA Polymerase) (EC 2.7.7.48).
DR; Pfam; PF01006; HCV_NS4A; 1.	DB Hepatitis C virus (isolate H) (HCV).	OS Viruses; ssRNA positive-strand viruses, no DNA stage; Flaviviridae;
DR; Pfam; PF01001; HCV_NS4B; 1.	DB Hepatitis C virus.	OC Hepatitis virus.
DR; Pfam; PF01506; HCV_NS5a; 1.	DB NCBI_TaxID=11108;	OC Hepatitis virus.
DR; Pfam; PF00271; helIcase_C; 1.	[1] _SEQUENCE FROM N_A. MEDLINE=905226; PubMed=1658800;	RT
DR; Pfam; PF00998; Viral_RdRp; 1.	RA Inchauspe G.; Zebede S.; Lee D.H.H.; Sugitani M.; Nassoff M., Prince A.M.;	
DR; Prodrom; PDI186052; HCV_NS1; 1.	"Genomic structure of the human prototype strain H of hepatitis C	
SMART; SM00487; DEXC07; 1.		
Polyprotein; Glycoprotein; Transferase; RNA-directed RNA polymerase; Core protein; Coat protein; Envelope protein; Helicase; ATP-binding; Transmembrane; Nonstructural protein; Hydrolase; Serine protease; 3D-structure.		
FT INIT_MET 1 1 REMOVED FROM CAPSID PROTEIN C BY THE 3D-structure.		
FT CHAIN 1 115 CAPSID PROTEIN C (POSSIBLE).		
FT CHAIN 116 191 MATRIX PROTEIN C (POSSIBLE).		
FT CHAIN 192 383 MAJOR ENVLOPSE PROTEIN E (POSSIBLE).		
FT CHAIN 384 729 NONSTRUCTURAL PROTEIN NS1/NS2 (POSSIBLE).		
FT CHAIN 730 1006 NONSTRUCTURAL PROTEIN NS2 (POSSIBLE).		
FT CHAIN 1007 1615 PROTEASE/HELIASE NS3 (POSSIBLE).		
FT CHAIN 1616 1862 NONSTRUCTURAL PROTEIN NS4A (POSSIBLE).		
FT CHAIN 1863 2013 NONSTRUCTURAL PROTEIN NS4B (POSSIBLE).		
FT CHAIN 2014 3011 RNA-DIRECTED RNA POLYMERASE (POSSIBLE).		
FT TRANSMEM 347 369 POTENTIAL.		
FT ACT_SITE 1083 1083 CHARGE RELAY SYSTEM (BY SIMILARITY).		
FT ACT_SITE 1107 1107 CHARGE RELAY SYSTEM (BY SIMILARITY).		
FT ACT_SITE 1165 1165 CHARGE RELAY SYSTEM (BY SIMILARITY).		
FT NP_BIND 1230 1230 ATP (POSSIBLE).		
FT SITE 1316 1319 DECH BOX (POSSIBLE).		
FT CARBOHYD 196 196 N-LINKED (GLCNAC. .) (POSSIBLE).		
FT CARBOHYD 209 209 N-LINKED (GLCNAC. .) (POSSIBLE).		
FT CARBOHYD 234 234 N-LINKED (GLCNAC. .) (POSSIBLE).		
FT CARBOHYD 305 305 N-LINKED (GLCNAC. .) (POSSIBLE).		
FT CARBOHYD 417 417 N-LINKED (GLCNAC. .) (POSSIBLE).		
FT CARBOHYD 423 423 N-LINKED (GLCNAC. .) (POSSIBLE).		
FT CARBOHYD 430 430 N-LINKED (GLCNAC. .) (POSSIBLE).		
FT CARBOHYD 448 448 N-LINKED (GLCNAC. .) (POSSIBLE).		
FT CARBOHYD 476 476 N-LINKED (GLCNAC. .) (POSSIBLE).		
FT CARBOHYD 532 532 N-LINKED (GLCNAC. .) (POSSIBLE).		
FT CARBOHYD 540 540 N-LINKED (GLCNAC. .) (POSSIBLE).		
FT CARBOHYD 556 556 N-LINKED (GLCNAC. .) (POSSIBLE).		
FT CARBOHYD 576 576 N-LINKED (GLCNAC. .) (POSSIBLE).		
FT CARBOHYD 623 623 N-LINKED (GLCNAC. .) (POSSIBLE).		
FT CARBOHYD 645 645 N-LINKED (GLCNAC. .) (POSSIBLE).		
FT CARBOHYD 2041 2041 N-LINKED (GLCNAC. .) (POSSIBLE).		
FT CARBOHYD 2077 2077 N-LINKED (GLCNAC. .) (POSSIBLE).		
FT CARBOHYD 2240 2240 N-LINKED (GLCNAC. .) (POSSIBLE).		
FT CARBOHYD 2364 2364 N-LINKED (GLCNAC. .) (POSSIBLE).		
FT CARBOHYD 2789 2789 N-LINKED (GLCNAC. .) (POSSIBLE).		
SO SEQUENCE 3011 AA; 327197 MW; 6588C9447FCEAF9 CRC64;	RN [1]	
Query Match 99.5%; Score 3602; DB 1; Length 3011;	RP	
Best Local Similarity 99.6%; Pred. No. 2.7e-248; 1; Mismatches 2; Indels 0; Gaps 0;	RX	
Matches 683; Conservative	RA	
SO	RA	

# Sequence Alignment

Mon Jun 21 17:31:26 2004

us-10-658-782-2.rsp

Page 1

Copyright (c) 1993 - 2004 GenCore version 5.1.6 Compugen Ltd.  
 OM protein - protein search, using sw model  
 Run on: June 21, 2004, 10:18:59 ; Search time 9.18516 Seconds  
 (without alignments)  
 Title: US-10-658-782-2  
 Perfect score: 361.9  
 Sequence: 1 MAPITAYAQQTGRGLLGCIT.....PAIPDREVLYREFDEMEEC 686  
 Scoring table: BLOSUM62  
 Gapop 10.0 , Gapext 0.5

Searched: 141681 seqs, 52070155 residues

Total number of hits satisfying chosen parameters: 141681

Minimum DB seq length: 0  
 Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%  
 Maximum Match 100%  
 Listing first 45 summaries

Database : SwissProt\_42.4\*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

## SUMMARIES

Result No.	Score	Query	Length	DB ID	Description
1	3602	99.5	3011	1 POLG_HCV1	P26644 h genome po
2	3513	97.1	3011	1 POLG_HCV1	P27958 h genome po
3	3426	94.7	3010	1 POLG_HCV1T	P26663 h genome po
4	3417	94.4	3010	1 POLG_HCV1	Q00369 h genome po
5	3408	94.2	3010	1 POLG_HCV1A	P26662 h genome po
6	3402	94.0	3010	1 POLG_HCV1A	P29466 h genome po
7	2989	82.6	3033	1 POLG_HCV1J	P26650 h genome po
8	2979	82.3	3033	1 POLG_HCV1B	P26651 h genome po
9	273	7.5	3898	1 POLG_HCVA	P19712 hog cholera
10	273	7.5	3898	1 POLG_HCVB	P21320 hog cholera
11	268.7	7.4	3988	1 POLG_BVDV	P19711 bovine virus
12	267.5	7.4	3898	1 POLG_BVDV	Q0199 bovine virus
13	227.5	6.3	3341	1 POLG_NCPA	P33515 m genome po
14	206	5.7	3140	1 POLG_PPVS	Q84334 p genome po
15	202	5.6	3125	1 POLG_PPVA	P17766 p genome po
16	201	5.6	3140	1 POLG_PPVA	P17767 p genome po
17	201	5.6	3140	1 POLG_PPVD	P13539 p genome po
18	200	5.5	3023	1 POLG_TMV	P09314 t genome po
19	199.5	5.5	3083	1 POLG_ZYMVR	Q89330 z genome po
20	199	5.5	3255	1 POLG_TEV	P31991 y genome po
21	199	5.5	3054	1 POLG_JAEVJ	P04317 t genome po
22	196	5.4	3432	1 POLG_JAEVJ	P32886 j genome po
23	195	5.4	3432	1 POLG_JAEVJ	P27395 j genome po
24	194	5.4	3391	1 POLG_DEN26	P29990 d genome po
25	194	5.4	3432	1 POLG_JAEV5	P19110 j genome po
26	193.5	5.3	3411	1 POLG_YBFV1	P0314 y genome po
27	193.5	5.3	3411	1 POLG_YBFV1	P19001 y genome po
28	192	5.3	3163	1 POLG_TUMVQ	Q02997 t genome po
29	192	5.3	3164	1 POLG_LMVE	P89761 genome po
30	191.5	5.3	3255	1 POLG_SBMVN	P21331 s genome po
31	189	5.2	3066	1 POLG_SBMVN	P2991 d genome po
32	187	5.2	3391	1 POLG_DEN27	P14340 d genome po
33	187	5.2	3391	1 POLG_DEN27	P02963 w genome po

## ALIGNMENTS

SEQ ID No: 2

RESULT 1

POLG\_HCV1  
 ID P2664;  
 AC P2664;  
 DT 01-AUG-1992 (Rel. 23, Created)  
 DT 01-AUG-1993 (Rel. 23, Last annotation update)  
 DE Genome polyprotein [Contains: Capsid protein C (Core protein) (P22); Envelope glycoprotein E1 (GP32); Envelope glycoprotein B2 (GP15); Nonstructural protein NS2 (P21); (GP48) (GP70) (NS1); Protein P7; (GP32); Nonstructural protein NS2 (P21); DE (EC 3.4.22.-); Protease/helicase NS3 (P70) (Hepacivirus)  
 DE (EC 3.4.21.98); Nonstructural protein NS4A (P4); Nonstructural protein NS5B (P66); (P70) (RNA-directed RNA polymerase) (EC 2.7.7.48)].  
 OS Hepatitis C virus (isolate 1) (HCV)  
 OC Viruses; ssRNA positive-strand viruses, no DNA stage; Flaviviridae;  
 OC Hepacivirus  
 OC  
 RN [1] \_TAXID=11104;  
 RN  
 RP SEQUENCE FROM N.A.  
 RX MEDLINE=91172826; PubMed=1848704;  
 RA Choo Q.-L., Richman K.H., Han J.H., Berger K., Lee C., Dong C., Gallegos C., Coit D., Medina-Selby A., Barr P.J., Weiner A.J., Bradley D.W., Kuo G., Houghton M.;  
 RA  
 RT "Genetic organization and diversity of the hepatitis C virus."  
 RL Proc. Natl. Acad. Sci. U.S.A. 88:2451-2455 (1991).  
 CC  
 CC - FUNCTION: The small proteins NS2A, NS2B, NS3A and NS4B are hydrophobic, suggesting a possible membrane-related function. NS3 and NS5 may play a role in the viral RNA replication.  
 CC  
 CC - CATALYTIC ACTIVITY: Hydrolysis of four peptide bonds in the viral precursor polyprotein, commonly with Asp or Glu in the P6 position. Cys or Thr in P1 and Ser or Ala in P1'.  
 CC  
 CC - CATALYTIC ACTIVITY: N nucleoside triphosphate = N diphosphate + (RNA) (N).  
 CC  
 CC - SUBUNIT: The virion of this virus is a nucleocapsid covered by a lipoprotein envelope. The envelope consists of two proteins: protein M and Glycoprotein E. The nucleocapsid is a complex of protein C and mRNA.  
 CC  
 CC - SIMILARITY: THE PROTEASE BELONGS TO PEPTIDASE FAMILY S29.

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EMBL; M32321; AA45676.1; -.  
 DR PIR; M3166; GNWIC3.  
 DR PDB; 1A1V; 16-FEB-99.  
 DR PDB; 1B1V; 25-NOV-98.  
 DR MEROPS; S29\_001; -.  
 DR MEROPS; U39\_001; -.  
 DR InterPro; IPR009003; Cyte\_Ser\_trypsin.  
 DR InterPro; IPR01410; DEAD.